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OCULAR HEMODYNAMICS IN NON-EXUDATIVE AGE RELATED MACULAR DEGENERATION

Non-Eksudatif Yaşa Bağlı Makula Dejenerasyonunda Oküler Hemodinami

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ABSTRACT

Purpose: To explore changes in retrobulbar ocular blood flow dynamics in patients with non-exudative age- related macular degeneration (ARMD).

Materials and Methods: 52 patients (M=28, F=24) with ARMD and 45 age-matched healthy controls (M=23, F=22) were included in our evaluation. Full ophthalmic examination and orbital color Doppler imaging was performed in both eyes. Peak systolic and end-diastolic velocities, resistive and pulsatility indices were considered as Doppler blood flow parameters in our evaluation. Central retinal, ophthalmic, temporal posterior ciliary and nasal posterior ciliary arteries measurements were taken.

Results: The mean age was 65.90 ± 2.05 (55-81) in ARMD and 60.95 ± 1.34 (55-70) in the control group. Pulsatility and resistive indices in ophthalmic arteries of ARMD patients were significantly higher than the control group. The peak systolic and end-diastolic velocities in nasal and temporal posterior ciliary arteries were significantly lower whereas pulsatility and resistive indices were significantly higher in ARMD compared to the control group. Peak systolic and end-diastolic velocities and resistive indices were significantly higher in ARMD cases, especially in posterior ciliary arteries supplying the choroid.

Conclusion: Perfusion defects of the retrobulbar vasculatures were significantly higher in ARMD compared to the healthy controls.

Key Words: Non-exudative age-related macular degeneration; choroidal perfusion, Doppler ultrasound, ocular hemodynamics.

ÖZET

Amaç: Amaç: Non-eksudatif yaşa bağlı makula dejenerasyonu bulunan hastalarda retrobulbar oküler kan akım hemodinamisindeki değişikliklerin değerlendirilmesi (ARMD).

Materyal ve Metod: ARMD'si olan 52 hasta (E=28, K=24) ve 45 tane yaşı uyumlu sağlıklı birey (E=23, K=22) çalışmaya dahil edildi. Her iki grupta, bilateral tam oftalmik muayene ve orbital renkli doppler görüntüleme gerçekleştirildi. Doppler kan akım parametreleri olarak pik sistolik ve end-diyastolik hızlar, rezistif ve pulsatilite indeksleri belirlendi. Santral retinal, oftalmik, temporal posterior siliyer ve nazal posterior siliyer arterlerde ölçümler yapıldı.

Sonuçlar: ARMD'li grupta yaş ortalaması 65.90 ± 2.05 (55-81), kontrol grubunda ise 60.95 ± 1.34 (55-70) idi. ARMD hastaların oftalmik arterlerinde, pulsatilite ve resistif indeksleri kontrol grubuna göre anlamlı yüksek bulundu. ARMD'li grupta kontrol grubuna göre, temporal posterior siliyer ve nazal posterior siliyer arterlerde, pik sistolik ve end-diyastolik hızlar anlamlı düşük, pulsatilite ve resistif indeksleri ise anlamlı yüksekti. Pik sistolik, end-diyastolik hızlar ve rezistif indeksler ARMD'li hastalarda, özellikle koroidi besleyen posterior siliyer arterlerde anlamlı yüksek bulundu.

Sonuç: Retrobulbar vasküler yapılarda perfüzyon defektleri, ARMD'li grupta kontrol grubuna kıyasla anlamlı yüksektir.

Anahtar Kelimeler: Yaşa bağımlı non-eksudatif makular dejenerasyon, koroidal perfüzyon, doppler ultrason, oküler hemodinami.

INDRODUCTION

Age related macular degeneration (ARMD) is a growing cause of visual loss among elderly with increased incidence in recent years. There are two types of ARMD: Non-exudative (Dry) and exudative (wet) forms. While the ethiopathogenesis is not clear, clinical features and natural progression of the disease are well-known (1). Degeneration of the retinal pigment epithelium, aging, genetic factors, sunlight exposure and primary ocular perfusion defects may play a role in pathogenesis of ARMD, however exudative and non-exudative macular degeneration has significant differences in clinical findings and disease progression.

The ARMD prevalence significantly increases with age (2,3). The relationship of smoking, alcohol abuse, hypertension, diabetes mellitus and genetic tendency have been defined as risk factors in various studies and it has been postulated that smoking might have an effect on development of ARMD due to the oxidative damage of the macula by a decrease in plasma oxygen concentration and retinal capacity (4,5). Gass demonstrated that macular disciform lesions may develop due to insufficieny of the choriocapillaris in submacular region (6). Localized angiosclerosis of the choriocapillaris may prevent nourishment of the retina and induce angiogenesis (7). High concentrations of Vascular Endothelial Growth Factor (VEGF), Basic Fibroblast Growth Factor (bFGF), Transforming Growth Factor-beta (TGF-β) and Platelet Derived Growth Factor (PDF) have been detected in vitreous and within the choroidal neovascular membranes (8). These findings support a presumed vascular etiology in ARMD. In this study, we aimed to explore the ocular perfusion defects in non-exudative ARMD patients by color doppler imaging.

MATERIALS AND METHODS

The study group was composed of 52 bilateral non-exudative type ARMD patients over 50 years old (28 males, 24 females). Forty five age-matched healthy subjects (23 males, 22 females) were included in the control group . ARMD patients who admitted to the outpatient clinics of our ophthalmology department and diagnosed as non-exudative macular degeneration, signed an informed consent for the imaging studies. The ophthalmic evaluation was performed by a retina specialist (MT) by stereoscopic fundus examination and fluorescein angiography. This study was approved by the Ethical Committee of Duzce University School of Medicine. Our exclusion criteria were diabetes mellitus, myocardial infarction, angina pectoris, systemic hypertension, cerebral and peripheral vascular diseases, hyperlipidemia and history of other ocular disease such as, high intraocular pressure, glaucoma or previous ocular surgery. The examinations were performed on both eyes by the same radiologist (AAS) at the doppler imaging center of the radiology department. The doppler ultrasonography was performed with real-time scanner (EUB-6500; Hitachi, Tokyo, Japan) with a 6-13 MHz linear transducer. The examinations were performed while the eyes closed without ocular movement, in an axial plane by applying gel over the eyelids in supine position. The patients were directed to look to the right side while examining the left eye and vice versa. The probe was bended about 10-15 degrees cranio-caudally to visualize the optic nerve. The mean examination interval was 20 minutes. Medium or lower flow settings were preferred while examining the central retinal arteries (CRA), whereas medium or higher flow settings were preferred for ophthalmic arteries (OA) and posterior ciliary arteries (PCA). The wall filters were adjusted to 30-50 Hz for CRA and 80-130 Hz for OA and PCA. Pulse repetition frequencies were adjusted to 1000-2000 for CRA and 2000-4000 for OA and PCA. The peak systolic (PSV), end-diastolic (EDV) velocities, resistivity (RI) and pulsatility (PI) indices of CRA, OA, nasal PCA (nPCA) and temporal PCA (tPCA) were measured. The doppler parameters of OA were measured at 25 mm posterior on nasal side of globe, where it crosses the optic nerve. The measurements of CRA were performed in the optic nerve and 0.3-1 cm proximally before its entrance to globe. The measurements of tPCA and nPCA were performed at 0.2-1 cm neighboring the optic nerve; bilaterally, posterior to the globe, if no flow has been detected at the defined localization, the measurements were performed 1.5-2 cm distal to the optic nerve near retina. Independent sample t-test was performed for the parametric criteria in both groups. Correlation coefficients were derived by Pearson's correlation coefficient. Statistical analysis was carried out using the Statistical Package for Social Science (SPSS)/PC 12.0 (SPSS INC, Chicago, IL).

Table 1: The distribution of the Mean doppler parameters of the ophthalmic arteries.

OA		N	Mean ± SE	SD	P	MD	SED	95% CI	
PSV	Patients	99	39.60±1.84	18.36	<0.001	-12,80	2.48	-17.75	-7.95
	Controls	89	52.40±1.63	15.37					
EDV	Patients	99	9.66±0.47	4.72	<0.001	-5.86	0.83	-7.50	-4.22
	Controls	89	15.52±0.70	6.58					
RI	Patients	99	0.75±0.02	0.20	0.008	0.06	0.02	0.01	0.10
	Controls	89	0.70±0.01	0.10					
PI	Patients	99	1.47 ± 0.03	0.31	<0.001	0.19	0.05	0.09	0.28
	Controls	89	1.28 ± 0.04	0.35					

OA: Ophthalmic artery; PSV: Peak systolic velocity; EDV: End diastolic velocity;RI: Resistivity index; PI: Pulsatility index; CI: Confidence Interval; SED: Standart Error Difference

RESULTS

The mean age was 65.9 ± 2.05 (55-77) in the non-exudative ARMD patients and 60.95 ± 1.34 (55-72) in the control group. There were no statistically significant differences in age and gender distribution of the ARMD patients and control group. Overall, 5 eyes in study group and 1 eye in control group could not been measured due to insufficient doppler frequency shift.

In OA of ARMD patients, PSV and EDV were significantly lower whereas PI and RI were significantly higher than the control group (p>0.001) (Table 1).

PSV, EDV and RI of CRA in the ARMD group was lower than the control group whereas PI was found higher in ARMD patients but the differences were statistically insignificant compared to the control group (p>0.05) (Table 2). PSV and EDV of tPCA and nPCA were significantly lower, but RI and PI were significantly higher in ARMD patients compared to the control group (p>0.001) (Table 3 and Table 4).

The PSV of all tested vessels were correlated with each other in non-exudative ARMD patients while there was not such a correlation in the control group (Table 5).

DISCUSSION

Exploring the ocular blood flow changes in ARMD, laser doppler flowmeter findings showed low choroidal blood flow and perfusion volume compared to the healthy controls (9). In doppler imaging of ocular blood flow, RI is the most important parameter

Table 2: The distribution of the Doppler parameters of the central retinal arteries.

CRA		No	Mean ± SE	SD	P	Mean difference	SE difference	95% CI	
PSV	PATIENTS	99	16.01 ± 0.76	7.60	>0,05	-1.63	0.98	-3.57	0.30
	CONTROLS	89	17.64 ± 0.59	5.56					
EDV	PATIENTS	99	4.13± 0.24	2.40	>0,05	-0.56	0.34	-1.24	0.11
	CONTROLS	89	4.70 ± 0.24	2.30					
RI	PATIENTS	99	0.73 ± 0.01	0.14	>0,05	-0.04	0.02	-0.09	0.01
	CONTROLS	89	0.77 ± 0.02	0.18					
PI	PATIENTS	99	1.38 ± 0.04	0.39	>0,05	0.08	0.06	-0.04	0.20
	CONTROLS	89	1.30 ± 0.04	0.42					

CRA: Central retinal artery; CI: Confidence Interval

Table 3: The distribution of the Doppler parameters of the temporal posterior ciliary arteries.

tPCA		No	Mean ± S.E	S.D	P	Mean difference	S.E. difference	95% C.I.	
PSV	PATIENTS	99	18.52 ± 0.82	8.16	<0.001	-4.22	1.04	-6.30	-2.16
	CONTROLS	89	22.74 ± 0.61	5.80					
EDV	PATIENTS	99	4.74 ± 0.23	2.31	<0.001	-3.60	0.44	-4.49	-2.75
	CONTROLS	89	8.36 ± 0.38	3.65					
RI	PATIENTS	99	0.73 ± 0.01	0.11	<0.001	0.08	0.01	0.04	0.11
	CONTROLS	89	0.65 ± 0.02	0.14					
PI	PATIENTS	99	1.80 ± 0.20	2.06	0.001	0.78	0.22	0.34	1.22
	CONTROLS	89	1.04 ± 0.03	0.30					

tPCA: temporal posterior central artery; CI: Confidence Interval

Table 4: The distribution of the Doppler parameters of the nasal posterior ciliary arteries.

nPCA		No	Mean SE	SD	P	Mean difference	SE difference	95% CI	
PSV	PATIENTS	99	16.25 ± 0.61	6.31	<0.001	-3.82	0.84	-5.50	-2.15
	CONTROLS	89	20.07 ± 0.14	5.15					
EDV	PATIENTS	99	3.37 ± 0.17	1.74	<0.001	-3.71	0.37	-4.44	-2.98
	CONTROLS	89	7.09 ± 0.33	3.17					
RI	PATIENTS	99	0.76 ± 0.01	0.14	<0.001	0.10	0.02	0.06	0.14
	CONTROLS	89	0.65 ± 0.01	0.14					
PI	PATIENTS	99	1.35 ± 0.03	0.30	<0.001	0.29	0.05	0.19	0.38
	CONTROLS	89	1.06 ± 0.04	0.34					

nPCA: nasal posterior ciliary arteries; CI: Confidence Interval

for vascular resistance for choroidal circulation. Previous studies indicate that RI reflects decreased vascular compliance supporting the choroidal hypoperfusion theory as posterior ciliary arteries (PCA) are the main arteries, feeding the choroid (10).

In our study RI for each tested vessel was found significantly higher in PCA of non-exudative ARMD patients compared to the controls (p>0.001), similarly Dimitrova et al reported an increased RI and PI in PCA however Friedman et al also reported decreased RI in PCA (10,11). In contrary, Ciulla et al. also showed that PSV and EDV of nPCA and tPCA were low and statistically significant in ARMD patients which were concordant with our results (12). In nonexudative patients, a decrease in EDV and PSV, and constant RI values indicate a decrease in blood flow of ciliary arteries (10).

In our study, OA Doppler measurements showed that PSV, EDV and RI was lower and PI was higher in ARMD patients compared to the control group. Ciulla et al found no significant difference among PSV, EDV and RI values of OA (12). Uretmen et al found high PI and RI for OA in patients with ARMD (13).

In CRA, similar to the findings of Friedman et al we found lower EDV and RI but higher PI (10). Although Ciulla and associates found that EDV was lower and RI was higher in CRA in ARMD patients (12). However, Polska et al reported that RI in the CRA does not correspond to retinal vascular resistance in healthy subjects (14). As macular area is primarily fed by the choroidal circulation, the specificity of RI of CRA is low for subfoveal and macular choroidal area blood flow. PSV and EDV of CRA usually do not correlate with the visual acuity in clinical significance of ARMD (12).

Our study showed perfusion deficits at the distal segment of PCA similar to CRA in ARMD patients. These findings suggest that there might be a diffuse perfusion defect in ocular ocular blood flow, and changes in CRA might be an autoregulatory response secondary to decreased ocular perfusion (12).

Mori et al compared the choroidal blood flow in early and late-stage ARMD patients with controls by pulsatile blood flow technique (15). They found that there was no difference in early-stage ARMD patients whereas the choroidal blood flow was significantly lower in late-stage patients.

In our study, PSV and EDV of PCAs were low and RI values were increased in nonexudative ARMD patients, which were concordant with previous studies (11,12). The decreased PSV and EDV indicate decreased perfusion in choroidal vessels. In addition to these doppler parameters, an increased RI, emphasize the vascular pathogenesis (hypoperfusion) in non-exudative ARMD as a causing factor in ethiopathogenesis which is yet undefined.

Harris et al studied the effects on retrobulbar circulation in elderly; PSV of OA was decreasing with age whereas, RI was increasing in both genders as in PCA, but in contrary, the changes in doppler parameters of CRA were independent of age (16). Some studies indicate effects of systemic blood pressure and intraocular pressure in ocular blood flow however, we excluded the patients with systemic hypertension and glaucoma in our study sample (17). Insulin-like factors, decrease in growth hormone and aging increase the vascular resistance by causing complete loss of elasticity in arterioles and decrease in elasticity in other vessels (18). Women lose cerebral vasoreactivity more than men, but estrogen replacement therapy decreases the effects of aging on arterial vasculature (19). In the presented study, there was no significant difference in retrobulbar blood flow between the males and females as mentioned in previous series.

Despite having different vascular diameter and wall thickness, our results suggest that changes in PSV are highly correlated with all tested retrobulbar vessels and indicate a decreased vascular compliance supporting the hypoperfusion theory.

The results of our study indicate significant changes in flow dynamics of the retrobulbar arteries, especially in posterior ciliary arteries in non-exudative ARMD patients. These Doppler parameters were supporting the ocular hypoperfusion theory (Hemodynamic Model) in pathogenesis of non-exudative ARMD.

In conclusion, retrobulbar color Doppler ultrasound imaging is a non-invasive and repeatable tool in evaluation of severity of the vascular involvement in follow-up of non-exudative ARMD patients. We believe, multicenter longitudinal studies with large number of patients may provide additional information to understand the role of choroidal and retrobulbar vascular hypoperfusion theory in development and progression of non-exudative ARMD in the future.

Table 5: The correlations of PSV and EDV of OA, CRA, tPCA and nPCA in both groups were shown.

	Patients			Controls		
PSV	N	R	p	N	r	p
OA- CRA	99	0.330	0.001	89	-0.033	>0.05
OA - tPCA	99	0.529	<0.001	89	0.202	>0.05
OA- nPCA	99	0.391	<0.001	89	-0.090	>0.05
CRA- tPCA	99	0.297	0.003	89	0.041	>0.05
CRA- nPCA	99	0.290	0.004	89	0.131	>0.05
tPCA- nPCA	99	0.721	<0.001	89	0.325	0.002
EDV						
OA- CRA	99	0.163	>0.05	89	-0.041	>0.05
OA - tPCA	99	0.070	>0.05	89	0.534	<0.001
OA- nPCA	99	-0.049	>0.05	89	-0.337	0.001
CRA- tPCA	99	0.026	>0.05	89	0.349	0.001
CRA- nPCA	99	-0.040	>0.05	89	0.488	<0.001
tPCA- nPCA	99	0.068	>0.05	89	0.366	<0.001

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